Summary of Safety and Effectiveness

MAY - 4 2011

I. Submitter Information - 21 CFR 807.92(a)(1):

Submitter: Affymetrix, Inc.
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Date Prepared: April 17, 2011

II. Name of Device and Classification - 21 CFR 807.92(a)(2):

Name: Affymetrix Gene Profiling Reagents

Classification: Class II

Product Code: OVA

III. Predicate Device - 21 CFR 807.92(a)(3):

Predicate Device: Affymetrix GeneChip® Microarray Instrumentation System

IV. Device Description - 21 CFR 807.92(a)(4):

The Affymetrix® Gene Profiling Reagents were designed for in vitro diagnostic use as an accessory to the GeneChip® MicroArray Instrumentation System. Affymetrix® Gene Profiling Reagents are intended for the preparation of labeled complementary RNA target from purified total RNA from fresh or frozen clinical tissue specimens for hybridization to Affymetrix® GeneChip® microarrays and the measurement of fluorescence signals of labeled RNA target using the Affymetrix GeneChip microarray instrumentation system. Intended for use with separately FDA-cleared Affymetrix GeneChip microarray assays specifying the use of the Affymetrix Gene Profiling Reagents.

The Affymetrix Gene Profiling Reagents consist of three kits.

Kit 1 is the RNA Control Kit consisting of Poly-A Control and Dilution Buffer. These reagents are designed to provide exogenous positive controls to monitor the entire target labeling process. The Poly-A Control and Dilution Buffer are provided with the kit to prepare the appropriate serial dilutions. After the appropriate dilution of the Poly-A Control, they are added to the total RNA and then amplified and labeled together. Examining the hybridization intensities of these controls on the array helps to monitor the amplification and labeling processes.

Kit 2 is comprised of the Transcript Synthesis and Labeling Kits A and B and includes enzyme mixes, labeling reagent, reaction buffers and purification reagents for the preparation of the

labeled cRNA target. Kit 2 is optimized specifically for producing amplified and biotinylated cRNA targets to hybridize to arrays for expression analysis.

Kit 3 is comprised of Transcript Detection Kits A, B and C and includes all of the reagents to perform fragmentation of the labeled cRNA target, prepare the hybridization cocktail (including Oligo B2 and hybridization controls) and process the arrays in the Affymetrix Fluidics Station 450. The arrays are then ready to be scanned by the Affymetrix GeneChip Scanner.

V. Intended Use/Indications for Use - 21 CFR 807.92(a)(5):

Affymetrix® Gene Profiling Reagents are intended for the preparation of labeled complementary RNA target from purified total RNA from fresh or frozen clinical tissue specimens for hybridization to Affymetrix® GeneChip® microarrays and the measurement of fluorescence signals of labeled RNA target using the Affymetrix GeneChip microarray instrumentation system.

Special Conditions For Use Statement(s):

Intended for use with separately FDA-cleared Affymetrix GeneChip microarray assays specifying the use of the Affymetrix Gene Profiling Reagents.

VI. Performance Data - 21 CFR 807.92(b):

A. Non-Clinical Test Summaries - 21 CFR 807.92(b)(1):

i. Analytical Performance:

1. Precision/Reproducibility

To demonstrate reproducibility studies were conducted in which three lots of Gene Profiling Reagents were tested

using 100 ng and 1000 ng of MAQC A and B total RNAs in quadruplicate by three different operators. Three lots of Pathwork® Expression 3'-Amplification One-Cycle Target Reagents were tested using 1000 ng of MAQC A and B total RNAs in quadruplicate by three different operators for comparison.

In addition, one lot of the Gene Profiling Reagents was tested using 100 ng and 1000 ng of MAQC A and B total RNAs in quadruplicate. One lot of the One-Cycle Reagent Kit was tested using 1000 ng of MAQC A and B total RNAs in quadruplicate for comparison. The testing was repeated on three different days.

The median probeset signal %CV from detected probesets was calculated both between lots and between days within a lot and is reported in Table 6-1 (a - d). The acceptance criterion of %CV less than 20% was met for all combinations.

Table 6-1

a - %CV between days within a lot for MAQC A

Data Sets	One-Cycle Days 1, 2 and 3 MAQC A	Gene Profiling 1000 ng Days 1, 2 and 3 MAQC A	Gene Profiling 100 ng Days 1, 2 and 3 MAQC A
Median CV%	7.97 %	7.17 %	7.03 %

b - %CV between days within a lot for MAQC B

Data Sets	One-Cycle Days 1, 2 and 3 MAQC B	Gene Profiling 1000 ng Days 1, 2 and 3 MAQC B	Gene Profiling 100 ng Days 1, 2 and 3 MAQC B
Median CV%	7.68 %	7.24 %	9.33 %

c - %CV between lots for MAQC A

Data Sets	One-Cycle Lots 1, 2 and 3 MAQC A	Gene Profiling 1000 ng Lots 1, 2 and 3 MAQC A	Gene Profiling 100 ng Lots 1, 2 and 3 MAQC A
Median CV%	8.70 %	9.54 %	8.74 %

d - %CV between lots for MAQC B

Data Sets	One-Cycle Lots 1, 2 and 3 MAQC B	Gene Profiling 1000 ng Lots 1, 2 and 3 MAQC B	Gene Profiling - 100 ng Lots 1,2 and 3 MAQC B
Median CV%	9.52 %	9.93 %	11.72 %

2. Repeatability

To demonstrate repeatability, the samples described in the Reproducibility section of this summary were used to calculate the median probeset signal %CV from detected probesets for the replicates. Table 6-2 (a - f) shows the results for all sets of replicates using the Gene Profiling Reagents and the One-Cycle Reagent Kits. The acceptance criterion for %CV less than 10% for Repeatability was met for all conditions.

Table 6-2

a - %CV for the replicates of 3 lots of the One-Cycle Reagent Kit, and one lot tested on 3 different days using 1000 ng of MAQC A.

Data Sets	Lot1 Day1 One-Cycle MAQC A	Lot1 Day2 One-Cycle MAQC A	Lot1 Day3 One-Cycle MAQC A	Lot2 Day1 One-Cycle MAQC A	Lot3 Day1 One-Cycle MAQC A
Median CV%	5.06%	4.55%	4.85%	3.67%	4.30%

b - %CV for the replicates of 3 lots of the Gene Profiling Reagents, and one lot tested on 3 different days using 100 ng of MAQC A.

Data Sets	Lot1 100ng Day1 MAQC A	Lot2 100ng Day1 MAQC A	Lot3 100ng Day1 MAQC A	Lot3 100ng Day2 MAQC A	Lot3 100ng Day3 – MAQC A
Median CV%	5.31%	5.81%	5.41%	4.24%	4.04%

c - %CV for the replicates of 3 lots of the Gene Profiling Reagents, and one lot tested on 3 different days using 1000 ng of MAQC A.

Data Sets	Lot1 1000ng Day1 - MAQCA	Lot2 1000ng Day1 - MAQCA	Lot3 1000ng Day1 - MAQCA	Lot3 1000ng Day2 - MAQCA	Lot3 1000ng Day3 - MAQCA
Median CV%	5.55%	4.38%	5.88%	4.54%	5.44%

d - %CV for the replicates of 3 lots of the One-Cycle Reagent Kit, and one lot tested on 3 different days using 1000 ng of MAQC B.

Data Sets	Lot1 Day1 One-Cycle MAQC B	Lot1 Day2 One-Cycle MAQCB	Lot1 Day3 One-Cycle MAQC B	Lot2 Day1 One-Cycle MAQC B	Lot3 Day1 One-Cycle MAQC B
Median CV%	4.57%	4.11%	4.35%	4.88%	4.64%

e - %CV for the replicates of 3 lots of the Gene Profiling Reagents, and one lot tested on 3 different days using 100 ng of MAQC B.

Data Sets	Lot1 100ng Day1 MAQC B	Lot2 100ng Day1 MAQC B	Lot3 100ng Day1 MAQC B	Lot3 100ng Day2 MAQC B	Lot3 100ng Day3 MAQC B
Median CV%	8.77%	4.42%	5.15%	5.46%	4.79%

f - %CV for the replicates of 3 lots of the Gene Profiling Reagents, and one lot tested on 3 different days using 1000 ng of MAQC B.

Data Sets	Lot1 1000ng Day1 MAQCB	Lot2 1000ng Day1 MAQCB	Lot3 1000ng Day1 MAQCB	Lot3 1000ng Day2 MAQCB	Lot3 1000ng Day3 MAQCB
Median CV%	5.74%	5.33%	4.23%	4.37%	5.64%

Repeatability was also demonstrated in the testing conducted at two external sites where eight replicates using 100 ng and 1000 ng of MAQC A and B total RNAs in batches of a minimum of 8 samples were tested. The median probeset signal %CV from detected probesets was calculated for the replicates and the acceptance criteria of % CV of < 10% was met for both sites.

3. Input Total RNA

The range for the amount of starting material to be used with the Gene Profiling Reagents was determined to be between 100 ng to 1000 ng (1µg) of total RNA. The reagents were tested in both internal and external studies using total RNA at the minimum and maximum amount of the range of input total RNA. The testing demonstrated the reagents performed as expected using 100 ng and 1000 ng of input total RNA and the amount of cRNA produced was sufficient for the hybridization of one microarray (≥ 20 µg).

The clinical study which utilized the Pathwork Tissue of Origin Test - Frozen used 200 ng of total RNA as the starting material. When the reagents were tested with 200 ng, the amount of cRNA produced was sufficient for the hybridization of one Pathchip™ microarray (≥ 15µg).

4. cRNA Yield

To demonstrate cRNA yield of the Gene Profiling Reagents testing was conducted internally by Affymetrix and at two external sites as part of the Design Validation.

The internal testing included 100 ng of total RNA from ten commercially available human tissues run in triplicate using the Transcript Synthesis and Labeling Kit (Kit 2). The test assessed the ability of the kit to yield ≥ 20 µg cRNA for greater than 90% of the total RNA samples tested and a cRNA concentration of ≥0.625 µg/µL. 100% (30/30) of the samples tested yielded greater than ≥ 20 µg cRNA and a cRNA concentration ≥0.625 µg/µL. Data is provided in Table 6-3.

The testing conducted at the two external sites included eight replicates using 100 ng and 1000 ng of MAQC A and MAQC B total RNAs in batches of a minimum of 8 samples.

The acceptance criterion for this study was cRNA yield of ≥96 % of samples prepared must produce ≥ 20 µg cRNA and cRNA concentration ≥0.625 µg/µL. All 32 samples (100%) at both sites achieved yields of ≥ 20 µg cRNA and cRNA concentration of ≥0.625 µg/µL.

Table 6-3

Sample ID	cRNA Concentration µg/µL	Adjusted cRNA yields (µg)	Average cRNA yields (µg)
Kidney Total RNA_R1	2.250	69.6	**67.1**
Kidney Total RNA_R2	2.112	65.4	
Kidney Total RNA_R3	2.141	66.3	
Pancreas Total RNA_R1	1.796	55.6	**54.2**
Pancreas Total RNA_R2	1.792	55.5	
Pancreas Total RNA_R3	1.664	51.5	
Heart Total RNA_R1	2.241	69.4	**69.2**
Heart Total RNA_R2	2.338	72.4	
Heart Total RNA_R3	2.126	65.8	
MAQCB Total RNA_R1	2.443	75.6	**74.4**
MAQCB Total RNA_R2	2.441	75.6	
MAQCB Total RNA_R3	3.009	72.1	
Liver Total RNA_R1	1.985	61.4	**57.1**
Liver Total RNA_R2	1.843	57.0	
Liver Total RNA_R3	1.705	52.8	
Breast Total RNA_R1	2.161	66.9	**62.2**
Breast Total RNA_R2	1.844	58.9	
Breast Total RNA_R3	1.965	60.8	
Testicle Total RNA_R1	2.207	68.3	**69.5**
Testicle Total RNA_R2	2.268	70.2	
Testicle Total RNA_R3	2.261	70.0	
HeLa Total RNA_R1	2.401	74.3	**73.7**
HeLa Total RNA_R2	2.277	72.8	
HeLa Total RNA_R3	2.390	74.0	
Thyroid Total RNA_R1	1.689	52.2	**50.5**
Thyroid Total RNA_R2	1.562	48.3	
Thyroid Total RNA_R3	1.644	50.8	
Skeletal Muscle Total RNA_R1	2.066	63.9	**62.3**

Sample ID	cRNA Concentration µg/µL	Adjusted cRNA yields (µg)	Average cRNA yields (µg)
Skeletal Muscle Total RNA _R2	2.043	63.2	
Skeletal Muscle Total RNA _R3	1.931	59.8	

5. Linearity/Assay Reportable Range

Not Applicable.

6. Traceability, Stability Expected Values (controls, calibrators or methods)

a. Performance of the Controls

Performance of the Poly-A Control, Oligo B2 and hybridization controls were evaluated by testing conducted internally at Affymetrix and at two external sites as part of Design Validation. The internal testing to evaluate the performance of the Poly-A Control, Oligo B2 and hybridization controls included three lots of Gene Profiling Reagents that were tested using 100 ng and 1000 ng of MAQC A and B total RNAs and tested in quadruplicate. The testing conducted at the two external sites included eight replicates using 100 ng and 1000 ng of MAQC A and B total RNAs in batches of a minimum of 8 samples.

In both studies .CEL files were generated by successful automatic gridding for all samples tested demonstrating that the Oligo B2 performed as expected. The analysis of the Poly-A Control showed the 3' AFFX-r2-Bs probe sets

for all three spikes (lys, phe and dap) were present. Signal intensities and r-squared values for the correlation of the 3' AFFX-r2-Bs signal intensities with the relative ratio for each spike, followed the relative concentration in the Poly-A Control mixture: lys < phe< dap and the r-squared values met the acceptance criteria of ≥ 0.900 for both studies. The 3' AFFX-r2 probeset for bioB was called present for all samples in both studies. The signal intensity for the hybridization controls (bioB, bioC, bioD and cre) followed the relative concentration in the mixture: bioB < bioC < bioD < cre for all samples tested in both studies. 100 % (80/80) of the samples passed the acceptance criteria for the performance of the controls in the internal study and 100% (64/64) in the external study.

In addition the performance of the controls was evaluated in the clinical studies. 45 total RNA samples were tested at each of the 3 clinical sites and 100% (135/135) passed the acceptance criteria for the Poly-A Control, Oligo B2 and hybridization controls. 16 total RNA samples from 16 frozen tissues were tested at one site and 100 % (32/32) passed the acceptance criteria for performance of the controls.

b. Stability Studies

Real-time stability studies are being conducted on the RNA Control Kit, the Transcript Synthesis and Labeling Kit and the Transcript Detection Kit. Based on the results of these studies, a shelf life from the date of manufacturing has been established for each of the Gene

Profiling Reagents. On-going stability studies are being conducted according to established procedures.

Open-vial stability studies have been completed for all reagent kits. Freeze-thaw stability studies have also been completed for the applicable reagents. The results of these studies support the freeze-thaw and open-vial stability recommended in the package inserts for the Gene Profiling Reagents.

c. Shipping Studies

Shipping studies under actual and simulated conditions have been conducted to confirm that the products have been designed, manufactured and packaged in such a way that they maintain transport storage conditions and packaging integrity. Additional shipping studies are being conducted to confirm that product performance is not affected under recommended storage and transportation conditions.

7. Detection Limit

Not applicable.

8. Assay Cut-Off

Not Applicable.

VII. Clinical Study Summary - 21 CFR 807.92(b)(2):

A. Comparison Studies:

i. Method Comparison:

The performance of the Affymetrix Gene Profiling Reagents was demonstrated utilizing a previously cleared expression assay on the Affymetrix GeneChip Microarray Instrumentation System. A two part prospective clinical study was conducted demonstrating performance of the Affymetrix Gene Profiling Reagents using the Pathwork® Tissue of Origin-Frozen Test (k080896) and the Affymetrix GeneChip® MicroArray Instrumentation System cleared for RNA analysis (k080995). Both studies evaluated the performance of the Pathwork® Tissue of Origin-Frozen Test with the Gene Profiling Reagents compared to performance of the assay demonstrated in K080896 using the One-Cycle Reagent Kit.

The first part of the prospective clinical study was conducted at 1 external site and included testing of 16 frozen tissues from RNA extraction to hybridization to the Pathchip™ microarray and scanning of the microarray on the Affymetrix GCS3000 Dx Instrument System. The 16 tissues, representing each of the 15 tumor types included in the Pathwork Tissue of Origin - Frozen cleared intended use, were tested twice using each of the Affymetrix Gene Profiling Reagents and the One-Cycle Reagent Kit included in Pathwork's K080896. The site was blinded to the available diagnosis of each tissue specimen. The resulting .CEL files were sent to Pathwork Diagnostics for analysis using proprietary Pathwork Tissue of Origin-Frozen algorithm. Pathwork Diagnostics was also blinded to the tissue sources.

The second part of the prospective clinical study was conducted at 3 clinical sites. The clinical study included the preparation of 45 total RNA samples using the Affymetrix Gene Profiling Reagents, with hybridization to the Pathchip™ microarray and scanning of the microarray on the Affymetrix GCS3000 Dx Instrument System. The resulting .CEL files were sent to Pathwork Diagnostics for analysis using proprietary

Pathwork Tissue of Origin-Frozen algorithm. The clinical sites and Pathwork Diagnostics were both blinded to the available diagnosis for each specimen. The study included 39 samples that had been tested using One-Cycle Kit reagents in the Pathwork Reproducibility study, as discussed in K080896 and 6 samples that had previously been tested with One-Cycle Kit reagents at one of the test sites. Results using One-Cycle Kit reagents were available from two sites for the 39 samples and 1 site for the 6 additional samples.

The acceptance criteria for both prospective studies were for the specimen processing specifications defined in the protocol to be met and the overall success rate for generating Tissue of Origin Test - Frozen results to be greater than 90%. Lastly, when data from these two studies were combined, the observed percent correct when using Gene Profiling Reagents could be no different from expected percent correct when using One-Cycle Reagent Kit ($\alpha = 0.05$).

Table 6-4 below shows the numbers of samples used in this comparison of One-Cycle Reagents and Gene Profiling Reagents.

TABLE 6-4 DISTRIBUTION OF SAMPLES USED FOR ANALYSIS

Protocol (unique samples)	Gene Profiling Reagents Reactions			One-Cycle Kit Reactions	
	Site 1	Site 2	Site 3	Site 1	Site 4
Total RNA Study (n = 45)	45	45	45	45	39
Tissue Study (n = 16)	32			32	
Total Reactions by Site	77	45	45	77	39
Total Reactions by Reagent	167			116	

In an integrated clinical analysis the performance of the Affymetrix Gene Profiling Reagents intended for in vitro diagnostic use were compared to the One-Cycle Reagent Kit intended for research use only which were utilized by Pathwork Diagnostics in the 510(k) for the Tissue of Origin Test - Frozen (K080896). The acceptance criteria for this analysis were for the observed percent correct when using IVD reagents should be no different from expected percent correct when using One-Cycle Kit reagents ($\alpha = 0.05$).

The results from this integrated analysis showed that the observed percent correct when using the Affymetrix Gene Profiling Reagents was no different ($\alpha = 0.05$) from the expected percent correct when using the One-Cycle Reagent Kit (95% bootstrap confidence limits are given by (-5.9%, 3.4%)). The acceptance criteria were achieved in support of substantial equivalence for the IVD and One-Cycle Kit reagents. The combined data from these studies demonstrated the performance of the TOO assay was comparable with both sets of reagents.

ii. Matrix Comparison:

Not Applicable.

iii. Clinical Sensitivity:

Not Applicable.

iv. Clinical Specificity:

Not Applicable.

v. Clinical Cut-Off:

Not Applicable.

vi. Expected Values/Reference Range:

Not Applicable.

vii. Other Clinical Supportive Data:

Not Applicable.

VIII. Conclusion

The submitted information in this premarket notification is complete and supports a substantial equivalence decision for the Gene Profiling Reagents.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Silver Spring, MD 20993

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Redwood Shores, CA 94065

MAY - 4 2011

Re: k103112
Trade/Device Name: Affymetrix® Gene Profiling Reagents
Regulation Number: 21 CFR 862.2570
Regulation Name: Instrumentation for Clinical Multiplex Test Systems
Regulatory Class: Class II
Product Code: OVA
Dated: April 22, 2011
Received: April 25, 2011

Dear Ms. Mende:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice

requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Maria M. Chan

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): k103112

Device Name: Affymetrix® Gene Profiling Reagents

Indications for Use:

Affymetrix® Gene Profiling Reagents are intended for the preparation of labeled complementary RNA target from purified total RNA from fresh or frozen clinical tissue specimens for hybridization to Affymetrix GeneChip® microarrays and the measurement of fluorescence signals of labeled RNA target using the Affymetrix GeneChip® Microarray Instrumentation System.

Intended for use with separately FDA-cleared Affymetrix GeneChip microarray assays specifying the use of the Affymetrix Gene Profiling Reagents.

Prescription Use___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) _k103112 _____